Complete Summary

GUIDELINE TITLE

Laboratory aspects. In: Guidelines for the programmatic management of drug-resistant tuberculosis.

BIBLIOGRAPHIC SOURCE(S)

Laboratory aspects. In: World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, Switzerland: World Health Organization (WHO); 2008. p. 36-49. [17 references]

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Drug-resistant tuberculosis (DR-TB), including:

- Multidrug-resistant tuberculosis (MDR-TB)
- Extensively drug-resistant TB (XDR-TB)

GUIDELINE CATEGORY

Diagnosis
Management
Prevention
Risk Assessment

CLINICAL SPECIALTY

Infectious Diseases
Pathology

INTENDED USERS

Clinical Laboratory Personnel
Health Care Providers
Health Plans
Hospitals
Managed Care Organizations
Nurses
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

- To describe standards for laboratory services needed to diagnose and treat drug-resistant tuberculosis (DR-TB) in the context of existing laboratory capacity and technological constraints
- To disseminate consistent, up-to-date recommendations for the diagnosis and management of multidrug-resistant tuberculosis in a variety of geographical, political, economic and social settings
- To enable access to comprehensive, up-to-date, technical and clinical information on the prevention and management of DR-TB and to encourage the implementation of known best practice
- To assist in the development of national policies to improve the diagnosis and management of DR-TB

TARGET POPULATION

Patients with suspected drug-resistant tuberculosis (DR-TB)

INTERVENTIONS AND PRACTICES CONSIDERED

1. Essential laboratory services and infrastructure
    - Mycobacterial and clinical laboratory services
    - Surveillance of prevailing drug resistance patterns and trends
    - Allocation of resources
    - Collecting and transferring specimens, cultures, and information
2. Organization of the laboratory network
    - Functions and responsibilities of level III laboratories
3. Transport of infectious substances
4. Identification of *Mycobacterium tuberculosis* (microscopy, culture)
5. Drug susceptibility testing (phenotyping, genotyping, rifampicin as a proxy for drug resistance)
6. Turnaround time for testing
7. Infection control and biosafety in the laboratory, including reassignment of personnel with human immunodeficiency virus (HIV) or pregnancy

8. Quality control and quality assurance

MAJOR OUTCOMES CONSIDERED

- Proficiency testing and validation of drug susceptibility testing data
- Transmission of drug-resistant tuberculosis (DR-TB)
- Time to diagnosis of infection

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The nominated lead author for each chapter used a limited evidence retrieval consisting of:

- Personal collection of publications and case reports
- Literatures searches using PubMed and other databases and search engines
- Existing guidelines, both from World Health Organization (WHO) and from other internationally recognized organizations
- Expert consensus during several group meetings for specific topics
- Unpublished data, for example data supplied to the Green Light Committee by their approved multidrug-resistant tuberculosis (MDR-TB) management projects

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus
Subjective Review

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The evidence was synthesized by each lead author, but a formal quality assessment was not used. Given the relatively small field of experts in managing drug-resistant tuberculosis, expert opinion was sought from several of the original researchers in the field. The evidence was not formally assessed or graded and there are no formal evidence summaries.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

A meeting of the World Health Organization (WHO) Guidelines Steering Group, together with several WHO advisers who had contributed to the 2006 edition, took place in April 2006. It was agreed that there was an urgent need for guidance on the best response to extensively drug-resistant tuberculosis (XDR-TB), based on the emerging evidence. The group identified the chapters to be reconsidered and the gaps to be addressed in this emergency update.

Of the total 18 chapters in the original guideline document, eight have been reviewed and substantially changed in response to the emerging evidence about multidrug-resistant tuberculosis and XDR-TB (chapters 1, 4, 5, 6, 7, 10, 12 and 18). One chapter is new (Chapter 19). The remaining chapters have undergone minor revisions to ensure consistency but have not been rewritten or had any new evidence included.

There was also a decision that a full review of the Guidelines will be started after the emergency update. The WHO Guidelines Review Committee was in place by January 2008 and had already developed draft Guidance for Emergency Guidelines which was used to guide best practice in the finalization of this emergency update.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

Cost is not explicitly considered as part of the recommendations, although the realities of human resources, socioeconomic issues and health system infrastructure are taken into consideration throughout the original guideline document.

Implementation of laboratory services for culture and drug susceptibility testing requires a reasonable balance between cost and turnaround time. Such services are most likely to be economically affordable and provide optimal results if based on direct delivery of specimens to a central mycobacteriology laboratory that has

large enough operational volume to ensure technical proficiency, has well-trained personnel and is properly equipped.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The chapters were each reviewed by at least one, and usually several, members of the Guidelines Reference Group, from both within the World Health Organization (WHO) Stop tuberculosis (TB) and human immunodeficiency virus (HIV) departments and outside external experts, as appropriate. One of the expert advisers on the Steering Group was commissioned to harmonize and review all the updated chapters. The remainder of the Steering Group also reviewed the whole document and provided extensive and detailed feedback.

The first draft of the guidelines was reviewed by the Steering Group at meeting held in February 2008. Other advisers at this meeting were Dr Malgosia Grzemska (WHO), Dr Suzanne Hill (WHO), Dr Tim Holtz (CDC, USA) and Dr Kathrin Thomas (WHO). Any outstanding issues were then resolved by e-mail to agree the final version. Other members of the group were asked to provide reviews at these later stages for particular issues.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Key Changes for the Emergency Update 2008 Compared to the 2006 Guideline

- Definitions of common terms used in laboratory issues are provided at the start of the chapter (Chapter 6 of the original guideline document).
- New recommendations for drug susceptibility testing (DST) to second-line drugs are proposed based on recent World Health Organization (WHO) policy guidance.
- References for regulations on how to transport infectious specimens internationally are provided.

Key Recommendations (*indicated updated recommendation)

- All patients suspected of drug-resistant tuberculosis (DR-TB) need access to laboratory services for adequate and timely diagnosis of DR-TB
- Laboratories should develop proficiency to isoniazid and rifampicin as a minimum and then consider DST of other drugs (see Figure 6.1 on the original guideline document)*
- Laboratories should develop DST of the fluoroquinolones and second-line injectable agents where adequate capacity and expertise exist*

- DR-TB strains can be transported safely across international borders if international procedures and guidelines are followed (see section 6.6 in the original guideline document)*
- Laboratories should follow all standardized protocols for infection control and biosafety
- Quality control and quality assurance should be in place for microscopy, culture and DST. Links with supranational TB reference laboratories are strongly encouraged.

Essential Laboratory Services and Infrastructure

Optimal management of DR-TB requires both mycobacterial and clinical laboratory services. At a minimum, the mycobacteriology laboratory service should provide culture, confirmation of *Mycobacterium (M.) tuberculosis* and DST of isoniazid and rifampicin. Clinical laboratory services should provide basic haematology, biochemistry, serology and urine analysis, required for the adequate evaluation and monitoring of patients (see the National Guideline Clearinghouse [NGC] summary of the WHO guideline, Initial evaluation, monitoring of treatment and management of adverse effects).

In addition to diagnostic services, laboratories supporting DR-TB control programmes have a critical role in surveillance of prevailing drug resistance patterns and trends. Surveillance of antituberculosis drug resistance is essential for providing information on the magnitude of and trends in drug resistance, for developing appropriate treatment modalities and for evaluating the impact of control programme interventions.

Adequate allocation of resources (human and financial) to laboratory services is essential to ensure availability of sufficient, adequately qualified and trained laboratory staff and a safe and functioning laboratory infrastructure with appropriate and well-maintained equipment and sufficient laboratory consumables.

DR-TB control programmes should have a rapid, reliable and safe means of collecting and transferring specimens, cultures and information from the patient and physician to appropriate levels of the laboratory service, and for returning the results.

Adequately equipped laboratory services to ensure safe handling of drug-resistant strains, especially during aerosol-producing procedures such as mycobacterial culture and DST, are paramount. Appropriate engineering controls, maintenance of essential laboratory safety equipment, and laboratory staff training are equally important.

Comprehensive systems for managing the quality of laboratory services are mandatory, including internal quality control and external quality assurance.

Organization of the Laboratory Network

Central reference laboratories supporting DR-TB control programmes should establish formal links with one of the supranational reference laboratories (SRLs)

to ensure adequate expert input on infrastructure development, budgeting and training. A sustained link with an SRL is also strongly recommended for DR-TB control programmes in order to maintain external quality assurance and validation of DST results. Documented first-line DST proficiency of central laboratories, preferably by one of the SRLs, is a prerequisite for applications by DR-TB control programme to the Green Light Committee (GLC).

DST of isoniazid and rifampicin is needed as a minimum in any DR-TB control programme; DST of other first-line antituberculosis drugs is also desirable, although less essential. In the initial phase of treatment for DR-TB, DST of second-line drugs is best left to supranational or other TB reference laboratories with documented capacity, expertise and proficiency. Once DST of first-line drugs operates at a consistently high level of proficiency, laboratories serving populations and patients with significant previous exposure to second-line drugs may consider extending their services to DST of second-line drugs (see "Transport of Infectious Substances" section below).

Routine DST of second-line drugs is not recommended unless the required laboratory infrastructure and capacity have been established, rigorous quality assurance is in place and sustainable proficiency has been demonstrated to isoniazid and rifampicin.

Transport of Infectious Substances

Given the risks associated with transport of specimens and/or cultures from patients suspected of having DR-TB, programmes should ensure appropriate systems for safe packaging and transportation of infectious materials.

International organizations such as the Universal Postal Union, the International Civil Aviation Organization and the International Air Transport Association have developed strict guidelines and procedures to facilitate the safe and expeditious shipment of infectious substances.

Exchange of *M. tuberculosis* cultures between countries (e.g., for diagnostic DST, retesting or proficiency testing) is always subject to international regulations, including national import and export regulations specific to individual countries.

Microscopy, Culture and Identification of *M. tuberculosis* in DR-TB Control Programmes

Microscopy

The main uses of microscopy for DR-TB are limited to assessing the initial infectiousness of patients, triaging specimens to different algorithms for culture and DST, and confirming that organisms growing on (or in) culture media are mycobacteria rather than contaminants.

As acid-fast bacilli (AFB) sputum smear microscopy is unable to distinguish between viable and non-viable bacilli, its utility for monitoring patient infectiousness and response to treatment is also limited. For example, even with adequate treatment, specimens from DR-TB patients may remain sputum smear-

positive after they become culture-negative, suggesting that the bacilli are non-viable. (Caution is nonetheless recommended for patients who are sputum smear-positive and culture-negative; they should be considered as possibly infectious and evaluated for progression of active disease.)

Culture

Quality of laboratory processing is of crucial importance. Delays in specimen transport, excessively harsh or insufficient decontamination, poor-quality culture media or incorrect incubation temperature can adversely affect the culture yield. Laboratory errors, such as mislabelling or cross-contamination between specimens during aerosol-producing procedures, may lead to false-negative or false-positive results. In this context, laboratory findings should always be correlated with the patient's clinical condition and any diagnostic test should be repeated if necessary. Low positive culture results on solid medium (<10 colonies) are not well correlated with clinical prognosis and should be interpreted with caution, especially if a single culture with low colony counts is reported. However, persistent positive cultures or any positive culture in the setting of clinical deterioration should be regarded as significant.

Identification of M. tuberculosis

Unless the species is confirmed as *M. tuberculosis*, mycobacterial isolates appearing phenotypically resistant to first-line drugs may represent infection with non-tuberculous mycobacteria (NTM) and not DR-TB. Treatment of NTM is entirely different from treatment of DR-TB. As a minimum, laboratories supporting DR-TB control programmes should be able to identify *M. tuberculosis* by conventional biochemical identification tests or at least two other methods that follow international guidelines.

Drug Susceptibility Testing

These guidelines strongly recommend that national TB control programmes (NTPs) develop the capacity to provide access to DST for any patient in whom resistance is considered likely.

The use of rapid rifampicin resistance testing is recommended in high-risk MDR-TB settings (including high-burden HIV settings); however, confirmation of MDR-TB by conventional DST is still regarded as the gold standard, and adequate laboratory capacity to ensure a quality-assured diagnosis of MDR-TB therefore remains a fundamental requirement.

No rapid molecular tests for detection of extensively drug-resistant TB (XDR-TB) are currently available; as a result, conventional and the newer liquid DST techniques are considered the most reliable methods for determining XDR-TB. Some of the newer liquid and agar techniques can determine the presence of XDR-TB within 14 days.

Rational Use of DST in DR-TB Control Programmes

Current WHO policy guidance on DST is as follows:

- Laboratory capacity to reliably detect MDR-TB through quality-assured DST of isoniazid and rifampicin resistance is a minimum prerequisite for DR-TB control programmes.
- Formal links with one of the laboratories in the SRL network are preferable to ensure adequate expert input on laboratory design, specimen and process flow, biosafety, maintenance of equipment and external quality assurance of DST result.
- Strategies for laboratory services in support of DR-TB control programmes should follow a systematic approach and take into account the constraints of DST outlined in the original guideline document. DST should be focused on those drugs for which a reliable and reproducible methodology is available.
- Routine DST of second-line drugs is not recommended unless the required laboratory infrastructure and capacity have been established, rigorous quality assurance is in place and sustainable proficiency has been demonstrated for isoniazid and rifampicin. In order to retain proficiency and expertise, it is recommended that second-line DST only be performed if at least 200 specimens from high-risk patients are expected per year.
- At this time, routine DST of drugs in groups 4 (ethionamide, protionamide, cycloserine, terizidone, *p*-aminosalicylic acid) and 5 drugs (clofazimine, linezolid, amoxicillin–clavulanate, thioacetazone, clarithromycin, imipenem) is not recommended as reliability and reproducibility of laboratory testing cannot be guaranteed.

Time for Testing and Reporting: Turnaround Time

To ensure rapid diagnosis of *M. tuberculosis* and DR-TB, laboratories should define standard turnaround times, which should be strictly followed.

Infection Control and Biosafety in the Laboratory

Mycobacteriological culture and DST generate high-concentration aerosols requiring biosafety level 3 containment precautions. Laboratory standards require the following essential measures to be in place and enforced:

- Appropriate and specific administrative controls (including good laboratory practice, standard operating procedures and accident management plans)
- Appropriate engineering controls functioning adequately as designed
- Personal protective equipment appropriate for the tasks being performed
- Proper waste management procedures
- Proper procedures for general laboratory safety (including physical, electrical and chemical safety)

Biosafety level 3 containment requires the strengthening of laboratory operations and safety programmes, specifically those related to laboratory design, the use of specialized equipment to prevent or contain aerosols and health surveillance of laboratory staff. Published guidelines on biosafety level 3 precautions should be rigorously followed and expert engineering consultation sought when establishing laboratory infrastructure for DST.

Health and medical surveillance of laboratory personnel involved in mycobacteriological culture and DST are strongly recommended. Surveillance should include a detailed medical history, targeted baseline health assessment,

monitoring of respiratory signs and symptoms, and a proactive plan for appropriate medical investigations when indicated.

Laboratory workers who choose to disclose that they are living with HIV, should be offered safer work responsibilities and should be discouraged from working with DR-TB specimens. Pregnant women should be reassigned until after childbirth and lactation.

Routine BCG vaccination is not recommended as a means of preventing DR-TB in laboratory workers. The use of infection control measures is discussed in more detail in Chapter 15 of the original guideline (see the NGC summary of the WHO guideline, Drug resistance and infection control).

Quality Control and Quality Assurance

A diagnosis of DR-TB has profound implications for the individual patient; therefore, accuracy of the laboratory diagnosis is crucial, and a comprehensive laboratory quality assurance programme must be in place to ensure the accuracy, reliability and reproducibility of DST results. Quality control or quality assurance procedures should be performed regularly as an integral part of laboratory operations.

Central reference laboratories involved in DR-TB control programmes should establish formal links with one of the laboratories in the SRL network to help ensure the quality of laboratory services and the validation of DST results.

The SRL network ensures DST standards by a system of external quality assurance that should preferably be established before the implementation of DR-TB control programmes. As a minimum, external quality assurance with an SRL should comprise:

- An initial assessment visit
- Proficiency testing with an adequate number of coded isolates
- Periodic rechecking of isolates obtained within the DR-TB control programme

As a minimum performance indicator, proficiency testing should correctly identify resistance to isoniazid and rifampicin in more than 90% in two out of three recent rounds of panels.

The SRL network is in agreement that panels for second-line proficiency testing should not include XDR strains of *M. tuberculosis*; rather, panels with different permutations of mono-resistance to second-line drugs are currently being developed, which will be compiled to allow reliable assessment of the overall capability of national reference laboratories to identify XDR-TB. Panels including isolates with second-line drug resistance will be made available through the SRL network in 2008.

CLINICAL ALGORITHM(S)

The original guideline document contains a clinical algorithm for a systematic approach to implementation of drug susceptibility testing under routine programmatic conditions.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Optimal use of standards for laboratory services needed to diagnose and treat drug-resistant tuberculosis (DR-TB) in the context of existing laboratory capacity and technological constraints may improve efficiency and timeliness in the identification of *Mycobacterium (M.)Â tuberculosis* infection and *M tuberculosis* drug susceptibility.

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.
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IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Chart Documentation/Checklists/Forms
Clinical Algorithm
Foreign Language Translations

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Laboratory aspects. In: World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, Switzerland: World Health Organization (WHO); 2008. p. 36-49. [17 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2008

GUIDELINE DEVELOPER(S)

World Health Organization - International Agency

SOURCE(S) OF FUNDING

UK Department for International Development
United States Agency for International Development

GUIDELINE COMMITTEE

Not stated

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

All of the above contributors completed a WHO Declaration of Interest form.

The following interests were declared:

Case Gordon declared that he is an unpaid advocate for patients with anti-TB drug resistance and for improved access to high-quality care. He declared that he has himself survived XDR-TB.

Tim Holtz declared that he is an unpaid technical adviser and member of the Scientific Advisory Board of a manufacturer of anti-TB products, to advise on the development of a new anti-TB compound that will be tested in clinical trials of MDR-TB regimens.

Salmaan Keshavjee declared that his employer received funding from a foundation associated with a manufacturer of anti-TB products to support the research and training unit that he is heading.

Carole Mitnick declared that she is serving as a paid member of the Scientific Advisory Board of a manufacturer of anti-TB products, to advise on the development of a new anti-TB compound that will be tested in clinical trials of MDR-TB regimens.

Michael Rich declared that his employer received funding from a manufacturer of anti-TB products, in support of his salary.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in English, Chinese, and French in Portable Document Format (PDF) from the World Health Organization Web site.

Print copies: Available from the WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland; Phone: +41 22 791 3264; Fax: +41 22 791 4857; E-mail: bookorders@who.int.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Executive summary. Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, Switzerland: World Health Organization (WHO); 2008. p. xi-xvi. Electronic copies: Available in Portable Document Format (PDF) from the World Health Organization Web site.

Print copies: Available from the WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland; Phone: +41 22 791 3264; Fax: +41 22 791 4857; E-mail: bookorders@who.int.

In addition, various forms, registers, and reports are available in the appendices of the original guideline document.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI Institute on August 28, 2009. The information was verified by the guideline developer on December 11, 2009.

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